



SEQUENCE LISTING

<110> Forman, Barry M.
Beard, Richard L.
Chandraratna, Roshantha A.

<120> Methods for Modulating FXR Receptor
Activity

<130> 17302

<140> 09/590,447

<141> 2000-06-09

<150> 60/138,986

<151> 1999-06-11

<160> 10

<170> FastSEQ for Windows Version 3.0

<210> 1

<211> 469

<212> PRT

<213> Rattus norvegicus

<400> 1

Met Asn Leu Ile Gly Pro Ser His Leu Gln Ala Thr Asp Glu Phe Ala
1 5 10 15
Leu Ser Glu Asn Leu Phe Gly Val Leu Thr Glu His Ala Ala Gly Pro
20 25 30
Leu Gly Gln Asn Leu Asp Leu Glu Ser Tyr Ser Pro Tyr Asn Asn Val
35 40 45
Gln Phe Pro Gln Val Gln Pro Gln Ile Ser Ser Ser Ser Tyr Tyr Ser
50 55 60
Asn Leu Gly Phe Tyr Pro Gln Gln Pro Glu Asp Trp Tyr Ser Pro Gly
65 70 75 80
Leu Tyr Glu Leu Arg Arg Met Pro Thr Glu Ser Val Tyr Gln Gly Glu
85 90 95
Thr Glu Val Ser Glu Met Pro Val Thr Lys Lys Pro Arg Met Ala Ala
100 105 110
Ser Ser Ala Gly Arg Ile Lys Gly Asp Glu Leu Cys Val Val Cys Gly
115 120 125
Asp Arg Ala Ser Gly Tyr His Tyr Asn Ala Leu Thr Cys Glu Gly Cys
130 135 140
Lys Gly Phe Phe Arg Arg Ser Ile Thr Lys Asn Ala Val Tyr Lys Cys
145 150 155 160
Lys Asn Gly Gly Asn Cys Val Met Asp Met Tyr Met Arg Arg Lys Cys
165 170 175
Gln Asp Cys Arg Leu Arg Lys Cys Arg Glu Met Gly Met Leu Ala Glu
180 185 190
Cys Leu Leu Thr Glu Ile Gln Cys Lys Ser Lys Arg Leu Arg Lys Asn
195 200 205
Val Lys Gln His Ala Asp Gln Thr Val Asn Glu Asp Ser Glu Gly Arg
210 215 220
Asp Leu Arg Gln Val Thr Ser Thr Thr Lys Leu Cys Arg Glu Lys Thr

225 230 235 240
Glu Leu Thr Val Asp Gln Gln Thr Leu Leu Asp Tyr Ile Met Asp Ser
245 250 255
Tyr Ser Lys Gln Arg Met Pro Gln Glu Ile Thr Asn Lys Ile Leu Lys
260 265 270
Glu Glu Phe Ser Ala Glu Glu Asn Phe Leu Ile Leu Thr Glu Met Ala
275 280 285
Thr Ser His Val Gln Ile Leu Val Glu Phe Thr Lys Arg Leu Pro Gly
290 295 300
Phe Gln Thr Leu Asp His Glu Asp Gln Ile Ala Leu Leu Lys Gly Ser
305 310 315 320
Ala Val Glu Ala Met Phe Leu Arg Ser Ala Glu Ile Phe Asn Lys Lys
325 330 335
Leu Pro Ala Gly His Ala Asp Leu Leu Glu Glu Arg Ile Arg Lys Ser
340 345 350
Gly Ile Ser Asp Glu Tyr Ile Thr Pro Met Phe Ser Phe Tyr Lys Ser
355 360 365
Val Gly Glu Leu Lys Met Thr Gln Glu Glu Tyr Ala Leu Leu Thr Ala
370 375 380
Ile Val Ile Leu Ser Pro Asp Arg Gln Tyr Ile Lys Asp Arg Glu Ala
385 390 395 400
Val Glu Lys Leu Gln Glu Pro Leu Leu Asp Val Leu Gln Lys Leu Cys
405 410 415
Lys Ile Tyr Gln Pro Glu Asn Pro Gln His Phe Ala Cys Leu Leu Gly
420 425 430
Arg Leu Thr Glu Leu Arg Thr Phe Asn His His Ala Glu Met Leu
435 440 445
Met Ser Trp Arg Val Asn Asp His Lys Phe Thr Pro Leu Leu Cys Glu
450 455 460
Ile Trp Asp Val Gln
465

<210> 2
<211> 484
<212> PRT
<213> Mus musculus

<400> 2
Met Val Met Gln Phe Gln Gly Leu Glu Asn Pro Ile Gln Ile Ser Leu
1 5 10 15
His His Ser His Arg Leu Ser Gly Phe Val Pro Asp Gly Met Ser Val
20 25 30
Lys Pro Ala Lys Gly Met Leu Thr Glu His Ala Ala Gly Pro Leu Gly
35 40 45
Gln Asn Leu Asp Leu Glu Ser Tyr Ser Pro Tyr Asn Asn Val Pro Phe
50 55 60
Pro Gln Val Gln Pro Gln Ile Ser Ser Ser Tyr Tyr Ser Asn Leu
65 70 75 80
Gly Phe Tyr Pro Gln Gln Pro Glu Asp Trp Tyr Ser Pro Gly Ile Tyr
85 90 95
Glu Leu Arg Arg Met Pro Ala Glu Thr Gly Tyr Gln Gly Glu Thr Glu
100 105 110
Val Ser Glu Met Pro Val Thr Lys Lys Pro Arg Met Ala Ala Ala Ser
115 120 125
Ala Gly Arg Ile Lys Gly Asp Glu Leu Cys Val Val Cys Gly Asp Arg
130 135 140
Ala Ser Gly Tyr His Tyr Asn Ala Leu Thr Cys Glu Gly Cys Lys Gly

145 150 155 160
Phe Phe Arg Arg Ser Ile Thr Lys Asn Ala Val Tyr Lys Cys Lys Asn
165 170 175
Gly Gly Asn Cys Val Met Asp Met Tyr Met Arg Arg Lys Cys Gln Glu
180 185 190
Cys Arg Leu Arg Lys Cys Arg Glu Met Gly Met Leu Ala Glu Cys Leu
195 200 205
Leu Thr Glu Ile Gln Cys Lys Ser Lys Arg Leu Arg Lys Asn Val Lys
210 215 220
Gln His Ala Asp Gln Thr Val Asn Glu Asp Asp Ser Glu Gly Arg Asp
225 230 235 240
Leu Arg Gln Val Thr Ser Thr Lys Phe Cys Arg Glu Lys Thr Glu
245 250 255
Leu Thr Ala Asp Gln Gln Thr Leu Leu Asp Tyr Ile Met Asp Ser Tyr
260 265 270
Asn Lys Gln Arg Met Pro Gln Glu Ile Thr Asn Lys Ile Leu Lys Glu
275 280 285
Glu Phe Ser Ala Glu Glu Asn Phe Leu Ile Leu Thr Glu Met Ala Thr
290 295 300
Ser His Val Gln Ile Leu Val Glu Phe Thr Lys Lys Leu Pro Gly Phe
305 310 315 320
Gln Thr Leu Asp His Glu Asp Gln Ile Ala Leu Leu Lys Gly Ser Ala
325 330 335
Val Glu Ala Met Phe Leu Arg Ser Ala Glu Ile Phe Asn Lys Lys Leu
340 345 350
Pro Ala Gly His Ala Asp Leu Leu Glu Glu Arg Ile Arg Lys Ser Gly
355 360 365
Ile Ser Asp Glu Tyr Ile Thr Pro Met Phe Ser Phe Tyr Lys Ser Val
370 375 380
Gly Glu Leu Lys Met Thr Gln Glu Glu Tyr Ala Leu Leu Thr Ala Ile
385 390 395 400
Val Ile Leu Ser Pro Asp Arg Gln Tyr Ile Lys Asp Arg Glu Ala Val
405 410 415
Glu Lys Leu Gln Glu Pro Leu Leu Asp Val Leu Gln Lys Leu Cys Lys
420 425 430
Met Tyr Gln Pro Glu Asn Pro Gln His Phe Ala Cys Leu Leu Gly Arg
435 440 445
Leu Thr Glu Leu Arg Thr Phe Asn His His Ala Glu Met Leu Met
450 455 460
Ser Trp Arg Val Asn Asp His Lys Phe Thr Pro Leu Leu Cys Glu Ile
465 470 475 480
Trp Asp Val Gln

<210> 3
<211> 472
<212> PRT
<213> Homo sapiens

<400> 3

Met Gly Ser Lys Met Asn Leu Ile Glu His Ser His Leu Pro Thr Thr
1 5 10 15
Asp Glu Phe Ser Phe Ser Glu Asn Leu Phe Gly Val Leu Thr Glu Gln
20 25 30
Val Ala Gly Pro Leu Gly Gln Asn Leu Glu Val Glu Pro Tyr Ser Gln
35 40 45
Tyr Ser Asn Val Gln Phe Pro Gln Val Gln Pro Gln Ile Ser Ser Ser

50	55	60	
Ser Tyr Tyr Ser Asn Leu Gly Phe Tyr Pro Gln Gln Pro Glu Glu Trp			
65	70	75	80
Tyr Ser Pro Gly Ile Tyr Glu Leu Arg Arg Met Pro Ala Glu Thr Leu			
85	90	95	
Tyr Gln Gly Glu Thr Glu Val Ala Glu Met Pro Val Thr Lys Lys Pro			
100	105	110	
Arg Met Gly Ala Ser Ala Gly Arg Ile Lys Gly Asp Glu Leu Cys Val			
115	120	125	
Val Cys Gly Asp Arg Ala Ser Gly Tyr His Tyr Asn Ala Leu Thr Cys			
130	135	140	
Glu Gly Cys Lys Gly Phe Phe Arg Arg Ser Ile Thr Lys Asn Ala Val			
145	150	155	160
Tyr Lys Cys Lys Asn Gly Gly Asn Cys Val Met Asp Met Tyr Met Arg			
165	170	175	
Arg Lys Cys Gln Glu Cys Arg Leu Arg Lys Cys Lys Glu Met Gly Met			
180	185	190	
Leu Ala Glu Cys Leu Leu Thr Glu Ile Gln Cys Lys Ser Lys Arg Leu			
195	200	205	
Arg Lys Asn Val Lys Gln His Ala Asp Gln Thr Val Asn Glu Asp Ser			
210	215	220	
Glu Gly Arg Asp Leu Arg Gln Val Thr Ser Thr Thr Lys Ser Cys Arg			
225	230	235	240
Glu Lys Thr Glu Leu Thr Pro Asp Gln Gln Thr Leu Leu His Phe Ile			
245	250	255	
Met Asp Ser Tyr Asn Lys Gln Arg Met Pro Gln Glu Ile Thr Asn Lys			
260	265	270	
Ile Leu Lys Glu Glu Phe Ser Ala Glu Glu Asn Phe Leu Ile Leu Thr			
275	280	285	
Glu Met Ala Thr Asn His Val Gln Val Leu Val Glu Phe Thr Lys Lys			
290	295	300	
Leu Pro Gly Phe Gln Thr Leu Asp His Glu Asp Gln Ile Ala Leu Leu			
305	310	315	320
Lys Gly Ser Ala Val Glu Ala Met Phe Leu Arg Ser Ala Glu Ile Phe			
325	330	335	
Asn Lys Lys Leu Pro Ser Gly His Ser Asp Leu Leu Glu Glu Arg Ile			
340	345	350	
Arg Asn Ser Gly Ile Ser Asp Glu Tyr Ile Thr Pro Met Phe Ser Phe			
355	360	365	
Tyr Lys Ser Ile Gly Glu Leu Lys Met Thr Gln Glu Glu Tyr Ala Leu			
370	375	380	
Leu Thr Ala Ile Val Ile Leu Ser Pro Asp Arg Gln Tyr Ile Lys Asp			
385	390	395	400
Arg Glu Ala Val Glu Lys Leu Gln Glu Pro Leu Leu Asp Val Leu Gln			
405	410	415	
Lys Leu Cys Lys Ile His Gln Pro Glu Asn Pro Gln His Phe Ala Cys			
420	425	430	
Leu Leu Gly Arg Leu Thr Glu Leu Arg Thr Phe Asn His His His Ala			
435	440	445	
Glu Met Leu Met Ser Trp Arg Val Asn Asp His Lys Phe Thr Pro Leu			
450	455	460	
Leu Cys Glu Ile Trp Asp Val Gln			
465	470		

<210> 4
<211> 462
<212> PRT

b6c
<213> Homo sapiens

<400> 4

Met Asp Thr Lys His Phe Leu Pro Leu Asp Phe Ser Thr Gln Val Asn
1 5 10 15
Ser Ser Leu Thr Ser Pro Thr Gly Arg Gly Ser Met Ala Ala Pro Ser
20 25 30
Leu His Pro Ser Leu Gly Pro Gly Ile Gly Ser Pro Gly Gln Leu His
35 40 45
Ser Pro Ile Ser Thr Leu Ser Ser Pro Ile Asn Gly Met Gly Pro Pro
50 55 60
Phe Ser Val Ile Ser Ser Pro Met Gly Pro His Ser Met Ser Val Pro
65 70 75 80
Thr Thr Pro Thr Leu Gly Phe Ser Thr Gly Ser Pro Gln Leu Ser Ser
85 90 95
Pro Met Asn Pro Val Ser Ser Ser Glu Asp Ile Lys Pro Pro Leu Gly
100 105 110
Leu Asn Gly Val Leu Lys Val Pro Ala His Pro Ser Gly Asn Met Ala
115 120 125
Ser Phe Thr Lys His Ile Cys Ala Ile Cys Gly Asp Arg Ser Ser Gly
130 135 140
Lys His Tyr Gly Val Tyr Ser Cys Glu Gly Cys Lys Gly Phe Phe Lys
145 150 155 160
Arg Thr Val Arg Lys Asp Leu Thr Tyr Thr Cys Arg Asp Asn Lys Asp
165 170 175
Cys Leu Ile Asp Lys Arg Gln Arg Asn Arg Cys Gln Tyr Cys Arg Tyr
180 185 190
Gln Lys Cys Leu Ala Met Gly Met Lys Arg Glu Ala Val Gln Glu Glu
195 200 205
Arg Gln Arg Gly Lys Asp Arg Asn Glu Asn Glu Val Glu Ser Thr Ser
210 215 220
Ser Ala Asn Glu Asp Met Pro Val Glu Arg Ile Leu Glu Ala Glu Leu
225 230 235 240
Ala Val Glu Pro Lys Thr Glu Thr Tyr Val Glu Ala Asn Met Gly Leu
245 250 255
Asn Pro Ser Ser Pro Asn Asp Pro Val Thr Asn Ile Cys Gln Ala Ala
260 265 270
Asp Lys Gln Leu Phe Thr Leu Val Glu Trp Ala Lys Arg Ile Pro His
275 280 285
Phe Ser Glu Leu Pro Leu Asp Asp Gln Val Ile Leu Leu Arg Ala Gly
290 295 300
Trp Asn Glu Leu Leu Ile Ala Ser Phe Ser His Arg Ser Ile Ala Val
305 310 315 320
Lys Asp Gly Ile Leu Leu Ala Thr Gly Leu His Val His Arg Asn Ser
325 330 335
Ala His Ser Ala Gly Val Gly Ala Ile Phe Asp Arg Val Leu Thr Glu
340 345 350
Leu Val Ser Lys Met Arg Asp Met Gln Met Asp Lys Thr Glu Leu Gly
355 360 365
Cys Leu Arg Ala Ile Val Leu Phe Asn Pro Asp Ser Lys Gly Leu Ser
370 375 380
Asn Pro Ala Glu Val Glu Ala Leu Arg Glu Lys Val Tyr Ala Ser Leu
385 390 395 400
Glu Ala Tyr Cys Lys His Lys Tyr Pro Glu Gln Pro Gly Arg Phe Ala
405 410 415
Lys Leu Leu Leu Arg Leu Pro Ala Leu Arg Ser Ile Gly Leu Lys Cys
420 425 430

Leu Glu His Leu Phe Phe Lys Leu Ile Gly Asp Thr Pro Ile Asp
435 440 445
Thr Phe Leu Met Glu Met Leu Glu Ala Pro His Gln Met Thr
450 455 460

<210> 5
<211> 147
<212> PRT
<213> *Saccharomyces cerevisiae*

<400> 5
Met Lys Leu Leu Ser Ser Ile Glu Gln Ala Cys Asp Ile Cys Arg Leu
1 5 10 15
Lys Lys Leu Lys Cys Ser Lys Glu Lys Pro Lys Cys Ala Lys Cys Leu
20 25 30
Lys Asn Asn Trp Glu Cys Arg Tyr Ser Pro Lys Thr Lys Arg Ser Pro
35 40 45
Leu Thr Arg Ala His Leu Thr Glu Val Glu Ser Arg Leu Glu Arg Leu
50 55 60
Glu Gln Leu Phe Leu Leu Ile Phe Pro Arg Glu Asp Leu Asp Met Ile
65 70 75 80
Leu Lys Met Asp Ser Leu Gln Asp Ile Lys Ala Leu Leu Thr Gly Leu
85 90 95
Phe Val Gln Asp Asn Val Asn Lys Asp Ala Val Thr Asp Arg Leu Ala
100 105 110
Ser Val Glu Thr Asp Met Pro Leu Thr Leu Arg Gln His Arg Ile Ser
115 120 125
Ala Thr Ser Ser Ser Glu Glu Ser Ser Asn Lys Gly Gln Arg Gln Leu
130 135 140
Thr Val Ser
145

<210> 6
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Junction between yeast GAL-4 DBD and human RXR
alpha LBD coding regions in GAL-L-RXR

<400> 6
gtatcgccgg aattcggtac cgtcgaggcc gtgcaggag 39

<210> 7
<211> 56
<212> DNA
<213> Artificial Sequence

<220>
<223> Junction between yeast GAL-4 DBD and rat RXR alpha
LBD coding regions in GAL-L-RXR

<400> 7
gtatcgccgg aattcgggct aaggaagtgc agagagatgg gaatgttggc tgaatg 56

<210> 8

b1 b2 b3
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> SV40 nuclear localization sequence

<400> 8
Ala Pro Lys Lys Lys Arg Lys Val Gly
1 5

<210> 9
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> Promoter region of plasmid TK-luc

<400> 9
ggttttccca gtcacgacgt tgtaaaaacga cggccagtgc caagcttgca tgccctgcagg 60
tcgactctag aggatccggc cccgcccagc gtcttgtcat tggcgaattc gaacacgcag 120
atgcagtcgg ggcggcgccg tcccaggtcc acttcgcata ttaaggtgac gcgtgtggcc 180
tcgaacacccg agcgaccctg cagcgcaccgg cttaacagcg tcaacagcgt gcccagatc 240
tctcgagtcg ggtactgttg gtaaaaatgga agacgccaaa aacataaaaga aaggcccggc 300
gccattctat cctctagagg atggaaccgc tggagagcaa ctgcataagg ctatgaagag 360

<210> 10
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Consensus S. cerevisiae UAGg response element

<400> 10
cgacggagta ctgtccctccg agct 24